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Low prevalence of pulmonary involvement in children with inflammatory bowel disease

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Summary
Background: Since extraintestinal sites of inflammation have been demonstrated in patients with Crohn's disease (CD) and ulcerative colitis (UC), both entities are regarded as systemic disorders. There are only scarce data on the prevalence of inflammatory bowel disease (IBD)-associated lung involvement in children.
Objectives: The aim of our study was to investigate pulmonary involvement in pediatric patients with IBD.
Material and methods: Fifty children with IBD (25 UC and 25 CD, mean age 14.2 ± 3.2 yrs) and 39 age-matched, healthy, control subjects were included in the study. Pulmonary function testing, methacholine bronchial challenge, fractional exhaled nitric oxide (FeNO) and high resolution computed tomography (HRCT) were used to detect functional and/or structural pulmonary involvement.
Results: There were no differences in spirometric parameters, lung volumes or lung diffusion capacity for carbon monoxide between IBD patients and control subjects. Highly significant differences were found in FeNO between CD, UC and control patients (mean 9.3 ± 3.3, 27.7 ± 14.8 and 16.6 ± 9.28, respectively; $p = 0.000$). Bronchial hyperresponsiveness was diagnosed in six IBD cases (14.6%). HRCT (performed in 32 patients from the study group) revealed mild bilateral bronchiectasis in one patient.
Conclusions: The prevalence of pulmonary involvement in children with IBD is low. Screening for pulmonary involvement in children and young adults with IBD may enable early detection of IBD-related pulmonary diseases which, seems to be notably more common in adult patients. Elevated FeNO could probably be regarded as a marker of airway involvement in non-smoking UC pediatric patients. This requires further studies.

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Abbreviations list

ATS	American Thoracic Society
BHR	bronchial hyperresponsiveness
CD	Crohn's disease
DLCO	diffusing lung capacity for carbon monoxide
ERS	European Respiratory Society
FeNO	fractional exhaled nitric oxide
FEV_1	forced expiratory volume in 1 s
FVC	forced vital capacity
HRCT	high resolution computed tomography
IBD	inflammatory bowel disease
MEF25	maximal expiratory flow at 25% of vital capacity
MEF50	maximal expiratory flow at 50% of vital capacity
PCDAI	Pediatric Crohn's Disease Activity Index
PFT	pulmonary function tests
PUCAI	Pediatric Ulcerative Colitis Activity Index
UC	ulcerative colitis
RV	residual volume
TLC	total lung capacity
TGV	thoracic gas volume

Introduction

Nowadays, Crohn's disease (CD) and ulcerative colitis (UC) are regarded as systemic disorders. Extraintestinal sites of inflammation have been found in various organs, including the respiratory system.

The features of the inflammation involving the respiratory system include lymphocytic, mononuclear or polymorphonuclear cell infiltration, as well as granuloma formation within the airway mucosa and in the lung parenchyma. These pathologic changes can lead to clinical manifestations such as bronchitis, bronchiolitis, interstitial pneumonitis, or pleuritis.[1,2] There are no precise data on the prevalence of inflammatory bowel disease (IBD)-associated lung involvement. The most common pulmonary manifestations in patients with IBD include: cough, pleuritic chest pain, sputum production and shortness of breath.[3] Some authors reported a relationship between both IBD duration and severity and the prevalence of pulmonary involvement.[4,5]

Data on CD related pulmonary disease in children are scarce.[6–10] They include mainly case reports and case series. Only 2 studies evaluated the prevalence, type and severity of pulmonary involvement in a prospective manner.[3,6] Surprisingly, we were not able to find any publications on pulmonary manifestations in children with UC. Diagnosis of pulmonary involvement in children with IBD seems important because most of these conditions are steroid-responsive.[11] Thus, early diagnosis gives the opportunity for effective treatment.

The aim of our study was to investigate pulmonary involvement in pediatric patients with IBD. The specific goals were as follows: 1) to compare the prevalence and type of pulmonary involvement in patients with CD and UC, 2) to compare the prevalence of lung parenchymal changes and bronchial involvement, 3) to evaluate the relationship between IBD duration and activity and the occurrence of pulmonary changes, 4) to assess the usefulness of different diagnostic methods in the evaluation of pulmonary abnormalities in children with IBD.

Material and methods

Study population

The study group consisted of 50 IBD patients (25 with UC and 25 with CD, mean age 14.2 $\pm$ 3.2 yrs) treated in the Department of Pediatric Gastroenterology and Nutrition, Medical University of Warsaw. Diagnosis of CD and UC was established in accordance with the Porto criteria.[12] Activity of the CD and UC was evaluated using the *Pediatric Crohn's Disease Activity Index* (PCDAI) and the *Pediatric Ulcerative Colitis Activity Index* (PUCAI). PCDAI score $\leq$ 10 for CD and PUCAI score $\leq$ 10 for UC were defined as remission. IBD duration was defined as time between the IBD diagnosis and inclusion into this study. Recruitment to the study did not affect treatment which had been continuously applied due to gastrointestinal symptoms (Table 1).

The control group, consisting of 39 healthy children (mean age 14.0 $\pm$ 3.5 yrs), was recruited concurrently.

In both study groups pulmonary function testing was applied to assess lung ventilation and gas exchange. BHR and FeNO were used as indirect markers of airway inflammation. Structural alterations in the lungs were evaluated with high resolution computed tomography (HRCT).

Pulmonary function tests

All patients underwent spirometry with flow-volume curve analysis (Spirometer Lungtest 1000, MES, Poland) as well as whole body-pletysmography (Bodypletysmograph Lungtest 1000, MES, Poland). All the pulmonary function parameters are presented as the number of standard deviations from reference value (z-score). Airway obstruction was diagnosed if z-score for FEV_1/FVC ratio was below $-$ 2. Abnormal small airways flow was diagnosed if MEF50 and MEF25 z-score was below -2.[13] Z-score for TLC lower than $-$ 2 was considered significant for a restrictive ventilatory defect. Lung diffusing capacity for carbon monoxide (DLCO) was measured by single-breath method using V-max 22 system (Sensor-Medics, USA). DLCO, adjusted to haemoglobin concentration, values below 80% and above 120% predicted were regarded as abnormal.

FeNO measurement

Fractional exhaled nitric oxide (FeNO) was measured with a chemiluminescence nitric oxide analyzer (NIOA, Sievers, USA) during single-breath exhalation and according to the ATS/ERS (American Thoracic Society/European Respiratory Society) guidelines.[14] FeNO values are reported in parts per billion (ppb). Concentrations higher than 35 ppb (for

Table 1 Characteristics of the study groups.

	CD $N = 25$	UC $N = 25$	Controls $N = 39$	P value
Mean age in years (SD)	14.3 (3.3)	14.1 (3.3)	14.0 (3.5)	NS
Male/female	16/9	10/15	20/19	NS
Systemic steroid use	3	9	0	
Other treatment				
Mesalazine	24	8	Not applicable	
Azatiopryne	18	9		
Sulfasalazine	2	15		
Weight in kg (SD)	53.4 (17.4)	50.0 (12.5)	52.8 (16.8)	NS
Height in cm (SD)	155.4 (30.4)	159.8 (14.3)	161.5 (16.7)	NS
Time from diagnosis in months (SD)	23.2 (20.68)	20.1 (19.4)	Not applicable	NS
Mean disease activity index (SD)	PCDAI Index 7.4 (11.2)	PUCAI Index 13 (15.7)	Not applicable	NS
Disease activity (number of patients)	Remission 21	Remission 11		
	Mild 2	Mild 12	Not applicable	
	Moderate 2	Moderate 2		

CD — Crohn's disease, UC — ulcerative colitis, SD — standard deviation, NS — not significant, PCDAI — Pediatric Crohn's Disease Activity Index, PUCAI - Pediatric Ulcerative Colitis Activity Index.

children $\leq$ 12 years) and higher than 50 ppb (for children $>$12 years) was considered abnormal.[15]

Bronchial hyperreponsiveness

Bronchial responsiveness was assessed by methacholine challenge test using dosimetric method, according to the ATS guidelines (Lungtest 1000, ISPA, MES, Poland). BHR was diagnosed at 20% FEV_1 fall compared to FEV_1 measured after dilutant (saline).[16]

High resolution computed tomography

HRCT was performed with a 16-row CT scanner (LightSpeed 16 General Electric, USA). The following parameters were applied: collimation - 1.0 mm, 1 s scanning time, current - 100 kV, 100 mA, matrix size 512 $\times$ 512. The CT image data were reconstructed with a high spatial frequency algorithm and viewed at a window level of − 450 HU and a window width of 1500 HU. Images were acquired at full inspiration and full expiration.

Statistical analysis

Statistical analysis was performed with STATISTICA software, version 9.0 (StatSoft, Tulsa, OK, USA). Variables were expressed as mean and standard deviation. Differences between continuous variables in groups were calculated with Kruskal—Wallis test. The Chi- squared test was used to assess the proportions of patients with abnormal results of different parameters in the study groups. Correlation between various indices of pulmonary involvement and diseases duration and activity was performed with Spearman's correlation test. All P values were 2-tailed and $P < 0.05$ was considered statistically significant.

Ethical considerations

The study protocol was accepted by Ethics Committee of Medical University of Warsaw (KB/96/2008) and a written informed consent was obtained from both the participants and their legal guardians.

Results

Characteristics of patients from the study and control groups is presented in Table 1. There were no smokers either in the study or in the control group. Seven patients from the study group (5 in CD and 2 in UC group) had positive history of atopy (asthma − one patient, atopic dermatitis —one patient, allergic rhinitis − five patients).

Six patients had complained of respiratory symptoms (chronic or recurrent cough or dyspnea) before entering the study. In all of these patients atopic diseases were diagnosed previously to the study onset.

Pulmonary function testing

The prevalence of ventilatory lung function impairment in IBD patients was low and not different from that found in control group (Table 2). A restrictive ventilatory pattern was demonstrated in only one patient (2%) (CD group). Airway obstruction was showed in two IBD patients (4%) (CD group) and in two patients (5.1%) from the control group. Small airway tests were abnormal in 13 (26%) subjects from the study group (8 and 5 in CD and UC group, respectively) and in 13 (33%) control subjects.

DLCO was abnormal in 9 (18%) (5 in CD, 4 in UC group) and 6 (15.3%) children from the study and the control group, respectively. There was no significant difference in the DLCO value between the study and control groups (Table 2).

No correlation between disease activity and any of PFT parameters or DLCO in study groups was found.

FeNO and BHR

Mean FeNO was 9.3 ppb (SD 3.3), 27.7 ppb (SD 14.8) and 16.6 ppb (SD 9,28) in CD, UC and control group, respectively. The differences in FeNO were highly significant ($p = 0.000$) and regarded all inter-group comparisons ($p = 0.000$)(Fig. 1). In 4 patients with UC, FeNO level exceeded the upper limit of normal.

Forty one children from IBD group underwent methacholine challenge test. Bronchial hyperresponsiveness was diagnosed in six cases (14.6%): 1 in CD and 5 in UC group. Two of these patients had positive history of atopy (allergic rhinitis).

Imaging studies

HRCT was performed in 32 patients from the study group. In all but one child, HRCT showed a normal parenchymal pattern. Mild bronchiectases in both upper lobes were found in one, 15 year-old, girl. She was asymptomatic and had no history of previous lung diseases.

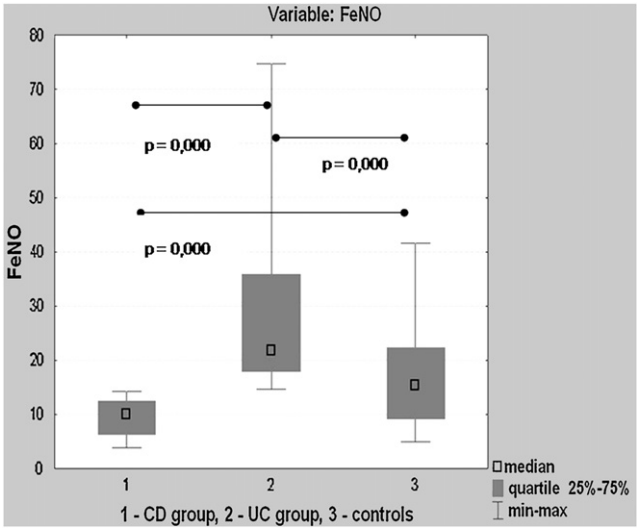

Figure 1 Fractional exhaled nitric oxide (FeNO) in Crohn's disease group (CD), ulcerative colitis group (UC), and controls.

Discussion

Our study showed that functional and structural pulmonary involvement in children with IBD is quite uncommon. As the study was based on the pre-defined, rigorous protocol and involved the largest group of children with IBD reported in the English literature, we believe, the presented results are fully reliable. Another advantage of our study might be the inclusion not only CD but also UC patients. To our knowledge, there were no previous studies assessing pulmonary involvement in children with UC.

Pulmonary function testing

The prevalence of ventilatory lung function impairment in IBD patients was surprisingly low. Interestingly, all patients with abnormal ventilatory pattern were found in the CD subgroup.

The most common spirometric abnormality, demonstrated in 26% of patients from the study group, was a decrease in MEF50 and MEF25 values. However, low MEF50 and MEF25 were also demonstrated in 33% of the control patients. These findings emphasize the importance of considering the results of measurements in a matched control group when interpreting the study outcomes.

The second most common abnormal finding in PFT was lung diffusion impairment as shown by decreased DLCO values in 9 (18%) children with IBD. However, there was neither a difference in DLCO value, nor in the proportion of patients with abnormal DLCO between study and control group. Thus, we believe it is not justifiable to conclude that decreased DLCO is a valuable or a specific marker of lung involvement in children with IBD.

There are several reasons making a comparison between our results and the results of previous studies difficult.

First, only one prospective study evaluating PFT in 26 pediatric patients with CD has been published.[6] However, this study was focused on differences in PFT results in patients with active vs. non-active disease. The authors could not show any difference in lung volumes and expiratory flows in these two groups.[6] In our study, there was no difference in PFT, measured in patients with active vs. non-active disease, neither was there a correlation between disease activity and any PFT parameter value. More in-depth comparison of these two studies is limited by fact that Munk et al. evaluated only CD patients and these authors did not include control subjects in their study.[6]

Table 2 Pulmonary function parameters in study groups.

Parameter	CD group mean (SD)	UC group mean (SD)	Control group mean (SD)	P value
FEV_1 z-score	−0.1 (1,0)	0.3 (0.97)	−0.2 (0.98)	NS
FVC z-score	0.01 (0.9)	0.3 (0.9)	−0.1 (0.9)	NS
FEV_1/FVC z-score	0.2 (1.2)	−0.3 (0.9)	−0.1 (0.96)	NS
MEF50 z-score	−0.6 (1.2)	−0.2 (1.2)	−0.7 (1.2)	NS
MEF25 z-score	1.1 (1.3)	−0.98 (1.2)	−1.3 (1.1)	NS
TLC z-score	1.0 (1.3)	1.3 (1.7)	0.2 (2.2)	NS
DLCO % of predicted value	94.5 (19.96)	90.3 (18.0)	101.8 (22.00)	NS

CD — Crohn's disease, UC — ulcerative colitis, FEV_1 — forced expiratory volume in 1 s, FVC — forced vital capacity, MEF50, 25 — maximal expiratory flow at 50, 25 percent of vital capacity (respectively), TLC — total lung capacity, DLCO — diffusing lung capacity for carbon monoxide.

Moreover, different disease activity scales were used. Nevertheless, on the basis of the report by Munk et al. and our study, it might be concluded that in children with IBD there is no relationship between disease activity and ventilatory lung function.

Second, in our study the abnormal PFT results were defined using z-score, which is the method recommended by ERS, particularly in children.[17] All previous publications, except those where the definition of normal range was not provided,[18] presented PFT measurements as percentage of normal value with abnormal results defined as those below a certain, pre-defined percent of predicted.[19] Of note, cut-off values ranging from 70 to 89% were applied in different studies. Particularly, a pre-defined cut-off percentage value of the FEV_1/FVC ratio (usually 70%), was used to diagnose airway obstruction.[20] This approach can be misleading, and result in underdiagnosis of airway obstruction. Hence, we believe our analysis may add to the existing literature, especially that the results were compared with well matched control group.

Although, the results of our study can be compared with the results of some adult studies, it should be stressed, that neither the prevalence, nor the pattern of pulmonary involvement in adults with IBD do necessarily reflects those observed in children. A comprehensive literature review published in 2007 summarized adult studies which were designed to compare PFT in IBD and control subjects.[21] Most of the analyzed papers have consistently found subtle or no spirometric abnormalities in IBD patients.[21] Three publications demonstrated considerable hyperinflation defined as increased RV, FRC or RV/TLC ratio as compared with control subjects.[22–24] In one paper, the prevalence of abnormal PFT results (FEV_1 and FVC) was significantly higher in IBD than in control subjects and positively correlated with disease activity.[25] In two other studies, small airway obstruction was observed and the authors found a significantly higher incidence of airflow limitation in the subgroup of IBD patients with active disease.[26,27]

Since 2007, several papers on pulmonary function in adults with IBD have been published. Yilmaz et al. showed that PFT were impaired in 22 of 39 patients with IBD (CD and UC) and the most prevalent change was decreased FEF 25%–75% (43.58%). Moreover, 7.7% of patients had an obstructive and 5.1% had a restrictive pattern of respiratory dysfunction. The differences in PFT results between the study and the control group were significant.[18] In contrast with these results, Ozyilmaz et al. found large airway obstruction (FEV_1/VC) only in 2 out of 33 patients with IBD (CD and UC) and no difference in PFT between the study and the control group.[20]

A number of studies have demonstrated a decreased DLCO in adults with IBD as compared to control subjects and it seems to be the most common abnormal finding in an IBD patients.[20,21,28] Moreover, a correlation between disease activity and DLCO has been found in some studies.[6,27,28] In only one study in children significantly lower DLCO in subjects with active as compared to non-active CD patients were demonstrated.[6] In our study, however, there was no difference in DLCO, measured in patients with active vs. non-active disease, neither was there a correlation between disease activity and DLCO value. Thus, we believe, the pattern of DLCO changes in children with active vs. non-active IBD requires further studies.

BHR and FeNO

The most prominent difference between CD, UC and control patients in our study was FeNO concentration. Differences in FeNO between CD and UC could reflect the different pathogenesis of these two entities. Th2-dependent inflammatory response is regarded as a typical feature of UC. Specific Th2 cytokines and chemo-attractants, e.g. IL-5, released in the inflammatory sites are responsible for the increased eosinophil count and activity and may lead to increased FeNO.[29,30] This seems to be confirmed in a study by Fireman et al.[31] The authors found an elevated eosinophil count in induced sputum from patients with UC. Conversely to UC, Th1 inflammatory type predominates in CD patients. Therefore, eosinophilic inflammation is not seen in the affected organs. Fireman et al. found an elevated CD4/CD8 ratio in induced sputum from CD patients, while the eosinophil count was within the normal range.[32]

The difference between FeNO in UC and CD patients could be affected by steroid treatment.[15] While as many as 36% of our UC patients received steroid treatment, as compared to only 12% of CD patients, we may speculate that if they had not been treated with steroids, FeNO in UC patients would have even been higher and the difference between UC and CD and control patients would have even been more significant. Since no data on FeNO levels in pediatric patients with IBD are available, our findings can be only compared to adult studies. Koek et al. showed a significant FeNO difference between CD, UC and control patients with highest FeNO values in the UC group. Moreover, they found a positive correlation with disease activity. These authors concluded, that increased FeNO in active IBD and its correlation with disease activity, provide evidence on the systemic nature of the IBD.[33]

Ozyilmaz et al. showed a difference in FeNO concentration between adult IBD patients with and without pulmonary involvement (mean values 32 and 24 ppb, respectively). However, the mean values in both groups were within normal limit.[20] The authors concluded that increased FeNO may be used for identifying patients with IBD who need further pulmonary evaluation. However, sensitivity and specificity analysis failed to determine cut-off value of FeNO levels which could reliably distinguish patients with and without pulmonary involvement.

Several studies in adults and one study in children assessed bronchial responsiveness in patients with IBD.[3] Mansi et al. reported BHR in as many as 10 from 14 children with CD participating in that study. The BHR was not related to CD duration or disease activity. The authors suggested that such a high prevalence of BHR in their patients could be explained by a higher prevalence of BHR in children as compared to adults.[3] In one adult study, Louis et al. demonstrated a significantly higher prevalence of BHR in IBD patients (45%) than in healthy controls (17%).[34] The results of our study are different than those reported by Mansi et al.[3] In our study group BHR was diagnosed in

only 6/41 (14.6%) of patients. Of note is the fact that Mansi et al. as well as some other authors, presented the results as provocating dose (PD).[3,35] According to ATS guidelines we used the provocative concentration (PC) that results in a 20% fall in FEV_1 (PC20) to measure bronchial responsiveness. This is because it is simple to calculate and avoids the complicated and controversial aspects of estimating a provocative dose (PD20).[16]

The positive methacholine challenge as an evidence of pulmonary involvement in IBD should be interpreted with caution because of high prevalence of positive results in the general population. In a recently published study Liem et al. found that diagnosis of BHR at the value of PC 20 $<$ 8 mg/ml yields with 52% positive results in healthy children.[36]

HRCT

We found a very low prevalence of pulmonary HRCT changes in children with IBD. Again, there are no data from children studies which could be compared to our observation. In adult IBD patients the prevalence of radiologic abnormalities was much higher. Mahadeva et al. revealed different types of pulmonary involvement (mostly bronchiectases, air trapping and "tree in bud" changes) in 14 of 17 investigated patients.[37] Spira et al. noted an abnormal HRCT pattern in 5 of 7 investigated patients.[38] In both studies, however, the HRCT was performed in symptomatic patients and this could probably explain the high prevalence of pulmonary changes. In a recent paper by Yilmaz et al., HRCT abnormalities were found in as many as 25/39 (64,1%) of adults with CD and UC. The most common findings were: peribronchial thickening, bronchiectases, ground glass opacities and emphysema.[18] In our study, the very low prevalence of HRCT abnormalities correlated with the absence or low incidence of abnormal PFTs and suggests that pulmonary involvement in children with IBD is significantly less common than in adults.

Conclusions

Although some abnormalities in parameters characterizing respiratory structure and function can be revealed in children with IBD, their prevalence is not higher than that found in healthy subjects. There are no evidences that disease activity and its duration are correlated with any of the lung function parameters. It seems that lung involvement in children with IBD is less common than in adult patients. Thus, we may hypothesize the first symptoms of pulmonary function impairment probably appear in late childhood, adulthood or in young adults. Screening for pulmonary involvement in these patient groups might be an important part of clinical assessment enabling an early detection of pulmonary dysfunction. Elevated FeNO could probably be regarded as a marker of airway involvement in UC pediatric, non-smoking patients. This requires further studies. Conversely to adult studies, decreased DLCO does not seem to be a reliable marker of lung involvement in children with IBD.

Author contributions

Joanna Peradzyńska- conception and design of the study, primary responsibility for protocol development, data analysis and interpretation, writing the manuscript, statistical analysis.

Katarzyna Krenke- conception and design of the study, primary responsibility for protocol development, data analysis and interpretation, writing the manuscript.

Joanna Lange- conception and design of the study, data acquisition, data analysis, writing manuscript.

Aleksandra Banaszkiewicz - conception and design of the study, data acquisition, data analysis, writing manuscript.

Izabella Łazowska-Przeorek - conception and design of the study, data acquisition, data analysis.

Andrzej Radzikowski — manuscript critical revision.

Marek Kulus - supervision of the design and execution of the study, manuscript critical revision, approval of the final version of the manuscript.

Conflict of interest statement

All authors declare nothing to disclose.

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